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13. ABSTRACT *(Maximum 200 words)*

Work has been completed on 4-substituted and 6-substituted N,N-Dimethylcarbamoyloxy derivatives in the imidazo[1,2-a]pyridinium series (six new compounds). Previously four 8-substituted compounds had been prepared. Work has been begun on the 7-substituted series. In each series the goal is to prepare the parent compound and three 2-substituted analogs containing methyl, isopropyl and phenyl substituents. In vitro biological assays have been performed on all available derivatives (eleven compounds). The 4- and 8-substituted analogs are more active than the 6-substituted compounds.

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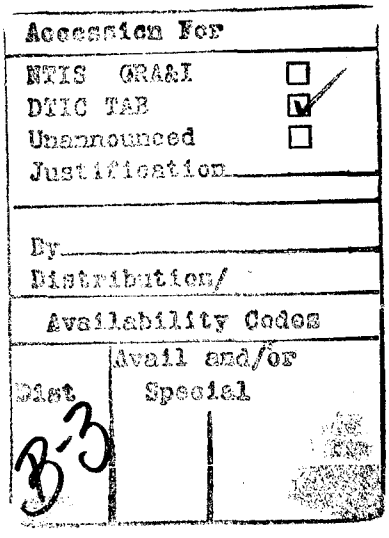


Richard W Clancy 6 June 95
PI - Signature Date

Table of Contents

I. Introduction.....1

II. Summary of Staffing.....2

III. New Compounds Prepared.....2

IV. Synthetic Methods.....4

V. Biological Activity.....6

VI. Future Plans.....8

VII. Experimental Section.....9

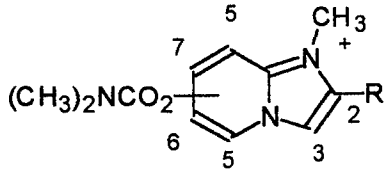
VIII. References.....18

I. Introduction

The development of prophylactic and therapeutic agents to prevent the lethal and incapacitating efforts of organophosphous (OP) acetylcholinesterase (AChE) inhibitors has remained a concern despite the development of international protocols to prohibit their military use. (1) As this year's events in Tokyo demonstrate, the preparation and delivery of the OP is within the capacity not only of non-complying governments, but also non-governmental entities.(2)

From a broader scientific perspective, additional understanding of the function of AChE and its therapeutic adjustment is important because of the crucial role of AChE in the function of the nervous system. Treatment of myasthenia gravis is accomplished by partial inhibition of AChE.(3) Furthermore, the postulate that some of the effects of Alzheimer's disease are due to a deficit in acetylcholine-mediated functions has led to interest in AChE inhibitors in therapy of Alzheimer's disease.(4)

Our studies began with the recognition that certain heteroaromaticquaternanry salts, derivatives of imidazo[1,2-a]pyridines in particular showed prophylatic activity towards soman.(5) In the preceding annual report we described the preparation of several 8-substituted and 4-substituted derivatives.(6) During the first quarter of the current year the 4-substituted series (3 additional compounds) and the 6-substituted (3 additional compounds) were completed. This leaves only the 7-substituted compounds unrepresented. In each series a range of 2-substituents was prepared, usually including the parent, methyl, isopropyl and phenyl derivatives.



R = H, CH_3, $CH(CH_3)_2$, Ph

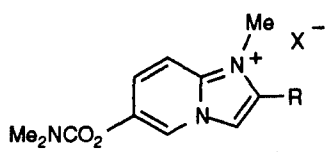
Synthesis of new compounds was temporarily discontinued in September, 1994 when the research associate resigned, but have now been resumed as will be described. Additional biological evaluation was continued during the September-November quarter providing preliminary in vitro data for all newly synthesized compounds. These results are discussed in Secion V.

II. Summary of Staffing

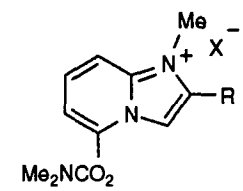
	Period	Effort %	Pay %
Richard J. Sundberg	1-June 94-31 Aug 94	33	33
	1-Sep 94-31 May 95	5	0
	1-June 95-30 June 95	33	33
Phouc Van Nguyen	1-June 94-31 Aug 94	100	100
Songjun Jiang	22-May 95-30 June 95	100	100
Janine Glavovic	1-June 94-25 Jan 95	100	100
	(unpaid leave 20 Jan 95-28 Feb 95)		

III. New Compounds Prepared

Six new compounds were prepared for submission during the year. The samples represent the completion of the 5- and 6-carbamates series. In both series the parent 1-methyl quarternary salts and the 2-methyl, 2-isopropyl and 2-phenyl were prepared. The 2-phenyl analog (BM 08648) of the 6-carbamates series was submitted earlier (Contract number: DAMD-17-89-C-9014).



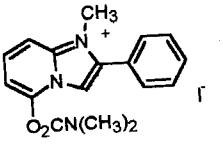
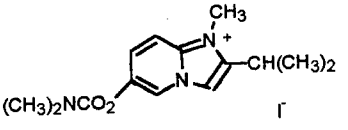
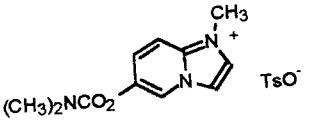
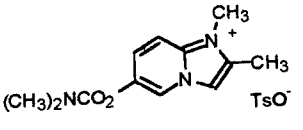
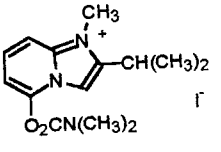
	R	X	
1	H	TsO	PN-III-268
2	Me	TsO	PN-IV-33
3	*i*-Pr	I	PN-III-240



	R	X	
4	H	Cl	PN-III-220
5	*i*-Pr	I	PN-IV-36
6	Ph	I	PN-III-236

The compounds are listed in Table 1 and details of the preparation are given in the Experimental Section.

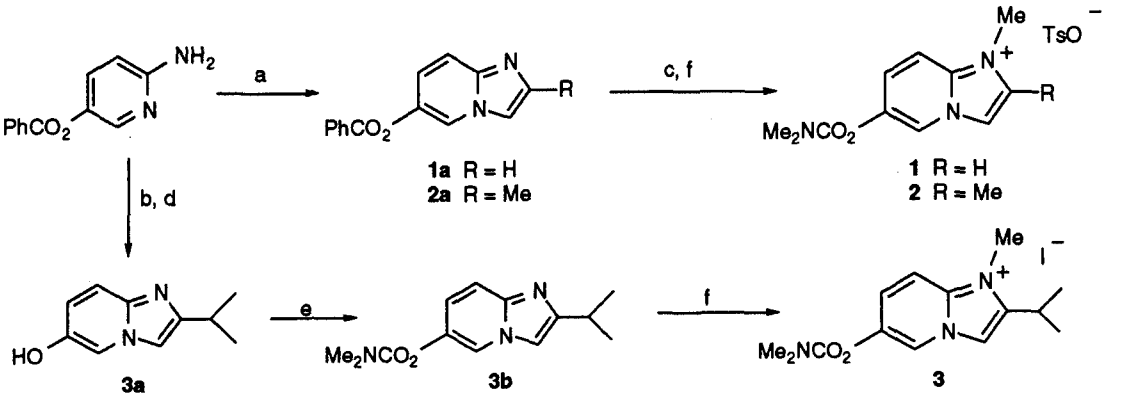
Table I. New Compounds Submitted

Our sample Number	WRAIR Bottle Number	WR Number	Date of Submission	Structure
PN-III-220	BN38865		8-7-94	
PN-III-236	BN38874		8-7-94	
PN-III-240	BN38883		8-7-94	
PN-III-268	BN40481	WR279951	15-9-94	
PN-IV-33	BN40507	WR279953	15-9-94	
PN-IV-36	BN40490	WR279952	15-9-94	

IV. Synthetic Methods

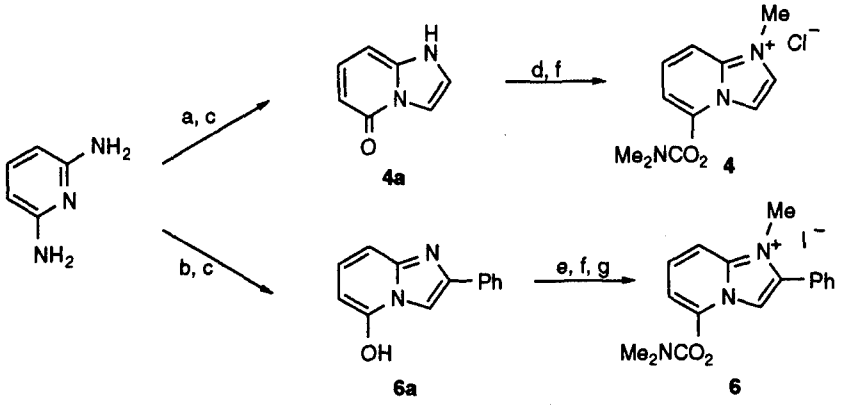
The synthetic routes for the compounds are outlined in Scheme 1, 2 and 3.

Scheme 1



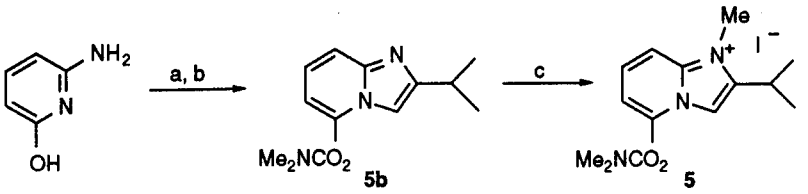
a) $ClCH_2CHO$ or $ClCH_2COCH_3$. b) $(CH_3)_2CHCOCH_2Br$. c) MeONa; Me_2NCOCl, C_5H_5N. d) NaOH. e) Me_2NCOCl, C_5H_5N, Δ. f) MeOTs or MeI.

Scheme 2



a) $ClCH_2CHO$. b) $PhCOCH_2Br$, Δ. c) 70% H_2SO_4, Δ. d) $NaNH_2$, MeI. e) NaH, DMF. f) $ClCONMe_2$. g) MeI, THF.

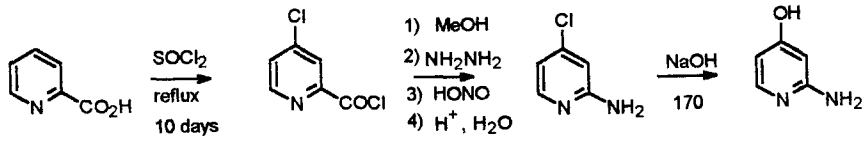
Scheme 3



a) NaH; $Me_2CHCOCH_2Br$. b) NaH; Me_2NCOCl. c) MeI

This methodology largely parallels that developed earlier for the 6- and 8-substituted series. However the 5-substituted series presented some special problems which appear to be associated with the existence of the compounds, at least under certain conditions in the oxo tautomeric structure **4a**. This required the use of a strong base to effect both the N-alkylation (step d, Scheme 2) and carbamoylation (step f, Scheme 2; step b, Scheme 3).

The 7-substituted series is now under investigation. There are surprisingly few entries to the 4-oxypyridin-2-amines needed as starting materials. The existing route to 4-hydroxypyridine-2-amine begins with picolinic acid.(7)



This route appeared sufficiently cumbersome to encourage explorartion of novel routes but preliminary efforts by Dr. Nguyen were not encouraging. As a result, Dr. Jiang has begun examining this route in the hopes of improving it. The initial results are very encouraging. Since it is difficult to conceive of an electrophilic or radical substitution mechanism which would result in the observed regioselectivity, we hypothesized that a combination of nucleophilic addition and oxidation was involved. Following this hypothesis the effect of added bromide and iodide as potential nucleophilic catalysts was examined. Both had substantial accelerating effects and in the presence of KI the reaction is complete in 3-4h. Preliminary runs have been done on each of the other steps and it appears they will be satisfactory for the preparation of the required 4-hydroxy-2-aminopyridine.

V. Biological Activity

While no direct evidence on the point is available it is reasonable to assume that the mechanism of action of the imidazo[1,2-a]pyridinium carbomates is analogous to that of pyridostigmine. That is, it is anticipated that they act as reversible AChE inactivators by carbamoylation of the active site serine. The postive charges present in both

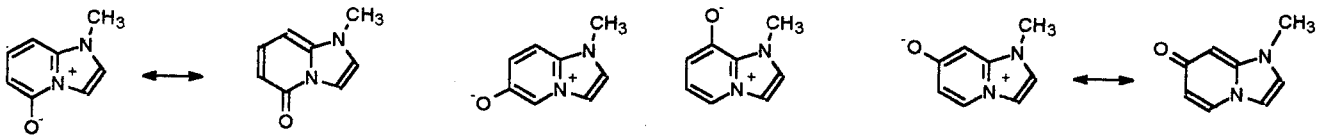
pyridostigmine and the imidazo[1,2-a]pyridinium salts are also presumably important in mimicking the charge of the natural substrate acetylcholine. If these presumptions are correct, measurement of AChE inhibition should be a predictive test of prophylactic activity. We therefore carry out an in vitro AChE inhibition assay following the method of Ellman using electric eel AChE.[8] Results from the 5-, 6- and 8-substituted imidazo[1,2-a]pyridinium salts are given in Table 2.

Table 2. Activity as Acetylcholinesterase Inhibitors.

Our Sample	WRBN	IC_{50}	R	Carbamoyloxy Substitution
PN-III-220	BN38865	0.04±0.01	H	5
PN-III-194	BN38856	0.03±0.01	CH_3	5
PN-IV-36	BN40490	0.014±0.005	$CH(CH_3)_2$	5
PN-III-236	BN38874	0.09±0.01	Ph	5
PN-III-268	BN40481	15.2±2.5	H	6
PN-IV-33	BN40507	31.4±12.4	CH_3	6
PN-III-240	BN3883	16.0±2.0	$CH(CH_3)_2$	6
PN-II-278	BN36049	0.04±0.005	H	8
PN-II-222	BN34830	0.075±0.005	CH_3	8
PN-III-28	BN36058	1.8±0.2	$CH(CH_3)_2$	8
PN-II-258	BN36030	2.5±0.3	Ph	8

From these results it appears that the 5- and 8-substituted compounds are substantially more active than the 6-substituted compounds. Under these conditions pyridostigmine has a IC_{50} of 0.7μM. The apparent sensitivity to position of substitution might be the result of several factors. It may originate in a preferred orientation in the binding site. There may also be an inherent reactivity factor which should correlate with the leaving group ability of the heterocycle. In this respect the 5- but not the 6- or 8- isomers benefit from additional reseonance stabilization. The 7-substituted system also has this stabilization available. If time permits upon completion of the synthesis and in vitro

bioassay we plan to explore these issues by modelling the fit of the compounds in the AChE active site.



To date no in vivo biological results have been provided for this series of compounds.

VI. Future Plans

Assuming the described experimental procedure will provide a basis for preparation of the 6-carbamoyloxy series of compounds, during the forthcoming months we will prepare as many of the compounds in the series as possible. Initial emphasis will be on the N,N-dimethylcarbamates with R^2 = H, CH_3, $CH(CH_3)_2$ and phenyl. When these are completed we will direct our attention to the N-methyl series. As the compounds become available, the in vitro acetylcholinesterase inhibition assays will be done. Experimental work is scheduled to terminate on December 31, 1995. During January, 1996, we will prepare the final report and during February - April we will prepare the results for publication and await the review of the final report. We expect to have completed the project by no later than May 31, 1996.

VII. Experimental Section

6-Benzoyloxyimidazo[1,2-a]pyridine (1a)

A mixture of 2-amino-5-benzoyloxypyridine[9] (6.52 g, 30.4 mmol) and chloroacetaldehyde (6.37 g, 36.5 mmol, 45% w/w in water) in acetone (150 mL) was gently refluxed. The reaction mixture was evaporated to dryness under aspirator pressure. The resulting residue was neutralized with satd $NaHCO_3$ solution and extracted with $CHCl_3$ (4 x 100 mL). The organic layers were washed with brine (2 x 100 mL), dried (anhyd Na_2SO_4), filtered and evaporated to dryness. Purification of the crude by column chromatography (silica gel, 20% of hexane in EtOAc) gave **1a** (3.34 g, 46 %) as a tan solid from EtOAc/hexane: mp 144-145 °C; R_f = 0.25 (EtOAc-hexane, 5:1); ^1H NMR ($CDCl_3$) δ 8.28 (d, 1 H, J = 2.1 Hz), 8.19-8.22 (m, 2 H), 7.51-7.70 (m, 6 H), 7.12 (dd, 1 H, J = 2.1, 9.6 Hz); ^{13}C NMR ($CDCl_3$) δ 164.87, 154.77, 143.76, 139.69, 134.63, 134.02, 130.20, 128.69, 121.13, 118.54, 117.80, 113.40. Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.47; H, 4.22; N, 11.75.

2-Methyl-6-benzoyloxyimidazo[1,2-a]pyridine (2a)

A mixture of 2-amino-5-benzoyloxypyridine (1.79 g, 8.36 mmol) and chloroacetone (0.77 mL, 9.2 mmol) in absolute ethanol (35 mL) was refluxed for 10 h. Two more portions of chloroacetone were added (0.3 mL each) over a period of 10 h. The solvent was then removed under reduced pressure. The resulting residue was treated with a satd $NaHCO_3$ solution. The aqueous mixture was extracted with $CHCl_3$ (4 x 25 mL) and dried (anhyd Na_2SO_4). Removal of solvent to dryness gave crude product, which was purified by column chromatography (silica gel, EtOAc-hexane, 2:1) to give **2a** (0.88 g, 41.8%) as off-white needles from EtOAc/hexane: mp 178-180 °C; R_f = 0.25 (EtOAc-hexane, 2:1); ^1H NMR ($CDCl_3$) δ 8.20 (ca, 1 H), 8.15-8.17 (m, 2 H), 7.62-7.68 (m, 1 H), 7.49-7.54 (m, 3 H), 7.34 (d, 1 H, J = 0.3 Hz), 7.05 (dd, 1 H, J = 2.1, 9.6 Hz), 2.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.87, 144.47, 143.26, 139.21, 133.88, 130.10, 128.60, 120.42, 117.95, 116.55, 110.51, 14.33. Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.25; H, 4.91; N, 11.22.

2-(2-Propyl)imidazo[1,2-a]pyridin-6-ol (3a)

A mixture of 2-amino-5-benzoyloxypyridine (0.89 g, 4.2 mmol) and 1-bromo-3-methylbutan-2-one[10] (0.75g, 4.6 mmol) in dry THF (15 mL) was refluxed for 16 h. Solvent was removed to dryness and the resulting residue was treated with aq 20% KOH solution. The mixture was stirred at 100 °C (oil bath temperature) for 1 h, then cooled and neutralized with concd HCl solution to give solid **3a** (0.52 g, 71 %): R_f = 0.43 ($CHCl_3$-MeOH, 9:1); ^{1}H NMR ($CDCl_3$) δ 7.76 (d, 1 H, J = 1.8 Hz), 7.19 (overlapped d, 1 H, J = 9.6 Hz), 7.18 (overlapped s, 1 H), 7.02 (dd, 1 H, J = 1.8, 9.6 Hz), 3.08 (septet, 1 H, J = 7.1 Hz), 1.32 (d, 6 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 151.97, 147.48, 140.81, 121.46, 115.01, 110.72, 107.87, 27.92, 22.46.

Imidazo[1,2-a]pyridin-5-ol (4a)

A mixture of 2,6-diaminopyridine (10.9 g, 0.1 mol) and chloroacetaldehyde (17.5 g, 45% w/w in water, 0.1 mol) in acetone (200 mL) was refluxed overnight. The reaction mixture was cooled and filtered to give a solid, which was washed with several portions of fresh acetone and dried under vacuum to afford 5-aminoimidazo[1,2-a]pyridine hydrochloride (16.9 g, 100%) as tan solid: ^{1}H NMR (DMSO-d_6) δ 8.45 (d, 1 H, J = 2.4 Hz), 8.08 (d, 1 H, J = 2.4 Hz), 7.99 (br s, 2 H), 7.69 (dd, 1 H, J = 7.8, 8.4 Hz), 7.00 (d, 1 H, J = 8.4 Hz), 6.49 (d, 1 H, J = 7.8 Hz).

A mixture of 5-aminoimidazo[1,2-a]pyridine hydrochloride (16.6 g, 97.8 mmol) in 70% H_2SO_4 solution was stirred at 120 °C (oil bath temperature) for 10 h. The reaction mixture was cooled and carefully neutralized with an aq 20% NaOH solution. Filtration of the mixture gave **4a** (10.93 g, 75.4%) as an olive green solid: R_f = 0.53 ($CHCl_3$-MeOH, 9:1); ^{1}H NMR (DMSO-d_6) δ 7.64 (d, 1 H, J = 2.1 Hz), 7.53 (d, 1 H, J = 2.1 Hz), 7.34 (dd, 1 H, J = 8.1, 8.4 Hz), 6.15 (d, 1 H, J = 8.1 Hz), 5.63 (d, 1 H, J = 8.4 Hz), 1.82 (br s, 1 H).

2-(2-Propyl)imidazo[1,2-a]pyridin-5-ol (5a)

To a cooled mixture of sodium hydride (1.46 g, 61.0 mmol, washed with pentane twice) in dry DMF (30 mL) was added slowly a solution of 1-amino-6-hydroxypyridine[11] (4.77 g, 40 mmol) in dry DMF (30 mL). The mixture was stirred in the cooling bath for 15 min., then warmed and stirred at room temperature for 3 h. A solution of 1-bromo-3-methylbutan-2-one (7.26 g, 44 mmol) in dry THF (20 mL) was added at once. The reaction mixture was stirred at 80 °C (oil bath temperature) overnight. Solvent was removed to dryness under reduced pressure. The resulting residue was partitioned between water and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (4 x 40 mL). The organic layers were washed with water, brine and dried (anhyd Na_2SO_4). Removal of solvent gave a crude product, which was purified by column chromatography (silica gel, $CHCl_3$-MeOH, 9:1) to give **5a** (3.32 g, 47.1%) as a tan solid: mp 163-165 °C; R_f = 0.5 ($CHCl_3$-MeOH, 9:1); ^1H NMR ($CDCl_3$) δ 7.51 (s, 1 H), 7.37 (t, 1 H, J = 8.4 Hz), 6.41 (d, 1 H, J = 8.4 Hz), 5.98 (d, 1 H, J = 8.4 Hz), 3.13 (septet, 1 H, J = 6.9 Hz), 1.39 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 156.84, 142.73, 139.94, 136.05, 103.39, 97.32, 89.31, 25.90, 21.62. Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.87; H, 6.88; N, 15.65.

2-Phenylimidazo[1,2-a]pyridin-5-ol (6a)

A solution of 2-bromoacetophenone (19.9 g, 0.1 mol) in dry THF (60 mL) was added dropwise to a mixture of 2,6-diaminopyridine (10.9 g, 0.1 mol) in THF (80 mL) at reflux temperature. The mixture was stirred at reflux overnight. 2,6-Diaminopyridine (3g) was added to the mixture which was refluxed for a further 5 h. The solvent was evaporated to dryness and the resulting residue was washed with Et_2O (3 x 100 mL) and then dissolved in methanol (150 mL). Concd HBr solution (3 mL) was added and the mixture was stirred at reflux for 30 min. Solvent was evaporated to dryness. The residue was neutralized with satd $NaHCO_3$ solution and the mixture was extracted with $CHCl_3$ (4 x 100 mL). The organic layers were washed with brine, dried (anhyd Na_2SO_4) and filtered via a column of silica gel, eluted with a mixture of 20% hexane in ethyl acetate to give 5-amino-2-phenylimidazo[1,2-a]pyridine (5.27 g, 25.2%): R_f = 0.44 (EtOAc-hexane, 4:1); ^1H NMR ($CDCl_3$) δ 7.94, (dd, 2 H, J = 1.4, 8.4 Hz), 7.64 (s, 1 H), 7.37-7.43 (m, 2 H), 7.29-7.34 (m, 1 H), 7.17 (d, 1 H, J = 8.8 Hz), 7.09 (dd, 1 H, J = 7.2, 8.8 Hz), 6.04 (dd, 1 H, J = 1.1, 7.2 Hz), 4.45 (br s, 2 H).

The treatment of 5-amino-2-phenylimidazo[1,2-a]pyridine (2.83 g, 13.5 mmol) with an aqueous 70% H_2SO_4 solution as described for **4a** gave **6a** (2.62 g, 92.2 %) as an olive green solid: R_f = 0.68 ($CHCl_3$-MeOH, 9:1); ^1H NMR (DMSO-d_6) d 8.24 (s, 1 H), 7.89 (d, 2 H, J = 7.8 Hz), 7.35-7.50 (m, 5 H), 6.24 (d, 1 H, J = 8.1 Hz), 5.72 (d, 1 H, J = 8.4 Hz).

6-(N,N-Dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (1b)

A mixture of **1a** (1.80 g, 7.6 mmol) and sodium methoxide (0.61 g, 11.3 mmol) in dry pyridine (50 mL) was stirred at 75 °C overnight. N,N-Dimethylcarbamoyl chloride (1.18 mL, 12.8 mmol) was added slowly via syringe. The reaction mixture was stirred for 10 h. Solvent was removed to dryness and the resulting residue was partitioned between a satd solution of $NaHCO_3$ and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (4 x 30 mL) . The organic layers were washed with brine, dried (anhyd Na_2SO_4) and filtered. Removal of solvent to dryness gave the crude product which was purified by column chromatography (silica gel, $CHCl_3$-MeOH, 50:1) to give **1b** (1.37g, 88.8%) as a pale yellow solid from EtOAc/hexane: mp 123-123.5 °C; R_f = 0.23 ($CHCl_3$-MeOH, 50:1); ^1H NMR ($CDCl_3$) δ 8.13 (ca, 1 H), 7.63 (d, 1 H, J = 1.2 Hz), 7.57 (d, 1 H, J = 9.6 Hz), 7.55 (s, 1 H), 7.03 (dd, 1 H, J = 2.1, 9.6 Hz), 3.11 (s, 3 H), 3.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.67, 140.21, 134.36, 121.70, 118.48, 117.39, 113.19, 36.86, 36.47. Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.67; H, 5.52; N, 20.54.

2-Methyl-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (2b)

The reaction of **2a** (3.3 g, 13.1 mmol) with sodium methoxide (1.06 g, 19.6 mmol) and N,N-dimethylcarbamoyl chloride (2.4 mL, 26.2 mmol) in dry pyridine (25 mL) at 95 °C (oil bath temperature) as described for **1b** gave **2b** (0.89 g, 31%) after purification by column chromatography (silica gel, gradient elution, 2-14% of ethanol in EtOAc). Decolorization of **2b** with charcoal in MeOH followed by recrystallization in EtOAc/hexane gave pale yellow needles: mp 133-134 °C; R_f = 0.40 (EtOAc-EtOH, 9:1); ^1H NMR ($CDCl_3$) δ 8.02 (d, 1 H, J = 2.1 Hz), 7.44 (d, 1 H, J = 9.6 Hz), 7.30 (s, 1 H), 6.97 (dd, 1 H, J = 2.1, 9.6 Hz), 3.10 (s, 3 H), 3.02 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.40, 144.20, 143.22, 139.78, 121.04, 117.98, 116.22, 110.34, 36.80, 36.42,

14.37. Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.33; H, 6.02; N, 19.15.

2-(2-Propyl)-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (3b)

A mixture of **3a** (0.21 g, 1.2 mmol) and N,N-dimethylcarbamoyl chloride (0.19 g, 1.8 mmol) in dry pyridine (10 mL) was stirred at 80 °C overnight. Solvent was then evaporated to dryness under reduced pressure and the resulting residue was partitioned between a satd $NaHCO_3$ solution and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (6 x 20 mL). The organic layers were washed with brine (2 x 20 mL), dried (anhyd Na_2SO_4), filtered and evaporated to dryness. Purification of the crude by column chromatography (silica gel; EtOAc-hexane, 4:1) afforded **3b** (0.21 g, 70%) as a thick oil: R_f = 0.29 (EtOAc-hexane, 4:1); ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1 H, J = 2.2 Hz), 7.39 (d, 1 H, J = 9.9 Hz), 7.20 (s, 1 H), 6.87 (dd, 1 H, J = 2.2, 9.9 Hz), 2.92-3.07 (overlapped m, 4 H), 2.91 (s, 3 H), 1.26 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 154.75, 154.20, 142.90, 139.51, 120.89, 118.06, 116.19, 108.15, 36.50, 36.19, 28.21, 22.20.

1-Methylimidazo[1,2-a]pyridin-5-one (4b)

A mixture of **4a** (2.68 g, 20 mmol) and sodium amide (1.09 g, 28 mmol) in dry DMF (30 mL) was stirred at room temperature for 30 min. Methyl iodide (1.62 mL, 26 mmol) was added dropwise by syringe and the mixture was stirred at room temperature for 2 h. Solvent was evaporated to dryness under vacuum and the resulting residue was partitioned between a satd $NaHCO_3$ solution and $CHCl_3$. Insoluble material was removed by filtration. The aqueous phase was extracted with $CHCl_3$ (5 x 50 mL). The organic layers were washed with brine (2 x 50 mL), dried (anhyd Na_2SO_4) and filtered. Removal of solvent yielded a crude product which was purified by column chromatography (silica gel, 5% of MeOH in $CHCl_3$) to afford **4b** (1.44 g, 48.6 %) as an off-white solid from acetone/hexane: mp 70-72 °C; R_f = 0.38 ($CHCl_3$-MeOH, 19:1); ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 1 H, J = 2.4 Hz), 7.44 (t, 1 H, J = 8.4 Hz), 6.97 (d, 1 H, J = 2.4 Hz), 6.01 (d, 2 H, J = 8.4 Hz), 3.68 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.97, 142.44, 136.98, 120.24, 108.46, 99.41, 83.47, 32.85.

2-(2-Propyl)-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (5b)

To an ice-cooled mixture of sodium hydride (0.5 g, 20.8 mmol, washed with pentane twice and dried under Ar) in dry THF (20 mL) was added via canula a solution of **5a** (2.64 g, 15 mmol) in dry THF (15 mL). The mixture was warmed up and stirred at 50 °C for 3 h. N,N-Dimethylcarbamoyl chloride (2.07 mL, 22.5 mmol) was then added by syringe. After being stirred at 50 °C for 5 h, the reaction mixture was evaporated to dryness and the resulting residue was partitioned between water and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$ (4 x 30 mL). The organic layers were washed with brine (2 x 30 mL), dried (anhyd Na_2SO_4) and filtered. Evaporation of the solvent gave crude product which was purified by column chromatography (silica gel, 20% of hexane in EtOAc) to give **5b** (2.83 g, 76.3 %) as colorless needles from EtOAc/hexane: mp 91-92 °C; R_f = 0.5 (EtOAc-hexane, 9:1); ^1H NMR ($CDCl_3$) δ 7.42 (dd, 1 H, J = 0.6, 9.0 Hz), 7.24 (s, 1 H), 7.17 (dd, 1 H, J = 7.5, 9.0 Hz), 6.58 (dd, 1 H, J = 0.6, 7.5 Hz), 3.23 (s, 3 H), 3.07-3.16 (overlapped m, 1 H), 3.08 (overlapped s, 3 H), 1.38 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 154.21, 151.81, 146.57, 140.48, 124.34, 113.36, 102.77, 101.28, 37.09, 36.72, 28.47, 22.41. Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.24; H, 6.97; N, 16.92.

2-Phenyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridine (6b)

Carbamoylation of **6a** (2.6 g, 12.3 mmol) with sodium hydride (0.2 g, 8.6 mmol) and N,N-dimethylcarbamoyl chloride (0.79 mL, 8.6 mmol) in dry DMF (25 mL) as described earlier for **5b** afforded a crude product which was purified by column chromatography (silica gel; 2% of MeOH in $CHCl_3$) to give **6b** (0.67 g, 42 %) as a yellow solid from EtOAc/hexane: mp 152-153 °C; R_f = 0.57 ($CHCl_3$-MeOH, 24:1); ^1H NMR ($CDCl_3$) δ 7.98 (d, 2 H, J = 7.2 Hz), 7.78 (s, 1 H), 7.51 (d, 1 H, J = 9.0 Hz), 7.43 (dd, 2 H, J = 7.2, 7.8 Hz), 7.32 (m, 1 H), 7.22 (dd, 1 H, J = 7.5, 9.0 Hz), 6.65 (d, 1 H, J = 7.5 Hz), 3.24 (s, 3 H), 3.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.68, 147.18, 145.85, 140.66, 133.63, 128.60, 128.00, 126.19, 125.17, 113.80, 103.55, 101.97, 37.16, 36.78. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.24; H, 5.40; N, 14.89.

General Procedure for Quaternization of Carbamates

A mixture of appropriate carbamate (1 equiv) and methyl *p*-toluenesulfonate or methyl iodide (1.5 equiv) in dry THF (or CH_3CN) was stirred at 60 °C overnight. Ether was added and the reaction mixture was cooled in ice. The precipitate was filtered and washed with several portions of ether to yield the product which was purified by recrystallization.

1-Methyl-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium *p*-Toluenesulfonate (1) PN-III-268

Following the general procedure for quaternization, the reaction of **1b** (0.103 g, 0.5 mmol) with methyl *p*-toluenesulfonate (0.14 g, 0.75 mmol) in dry THF (5 mL) gave **1** (0.19 g, 97 %) as a white solid: mp 176-177 °C; IR $(KBr)_{\nu max}$ 3138, 3045, 1732, 1184 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (d, 1 H, J = 1.8 Hz), 8.65 (d, 1 H, J = 1.8 Hz), 8.13 (d, 1 H, J = 1.8 Hz), 7.99 (d, 1 H, J = 9.6 Hz), 7.79 (d, 2 H, J = 8.1 Hz), 7.66 (dd, 1 H, J = 1.8, 9.6 Hz), 7.13 (d, 2 H, J = 8.1 Hz), 4.12 (s, 3 H), 3.09 (s, 3 H), 3.01 (s, 3 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.23, 143.98, 143.22, 139.08, 136.96, 130.66, 128.55, 127.47, 125.81, 122.85, 116.10, 110.61, 36.94, 36.60, 34.60, 21.22. Anal. Calcd for $C_{18}H_{21}N_3O_5S$: C, 55.23; H, 5.41; N, 10.73. Found: C, 55.49; H, 5.40; N, 10.72.

1,2-Dimethyl-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium *p*-Toluenesulfonate (2) PN-IV-33

Following the general procedure for quaternization, the treatment of **2b** (55 mg, 0.25 mmol) with methyl *p*-toluenesulfonate (70 mg, 0.37 mmol) in dry THF (2 mL) gave **2** (95 mg, 94 %) as a white solid from MeOH/Et_2O: mp 223-224 °C ; IR $(KBr)_{\nu max}$ 3113, 3049, 1716, 1184 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.97 (d, 1 H, J = 1.9 Hz), 8.18 (d, 1 H, J = 9.8 Hz), 8.15 (s, 1 H), 7.92 (dd, 1 H, J = 1.9, 9.8 Hz), 7.46 (d, 2 H, J = 7.9 Hz), 7.08 (d, 2 H, J = 7.9 Hz), 3.90 (s, 3 H), 3.08 (s, 3 H), 2.95 (s, 3 H), 2.49 (s, 3 H), 2.27 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 152.93, 145.85, 142.44, 137.28, 137.10, 135.84, 129.37, 127.79, 125.32, 121.56, 112.42, 110.68, 36.43, 36.09, 30.79, 20.59, 9.22. Anal. Calcd for $C_{19}H_{23}N_3O_5S$: C, 56.28; H, 5.72; N, 10.36. Found: C, 56.37; H, 5.78; N, 10.36.

1-Methyl-2-(2-propyl)-6-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (3) PN-III-240

Following the general procedure for quaternization, **3b** (1.27 g, 5.1 mmol) was reacted with an excess of methyl iodide in dry THF to give **3** (1.65 g, 82.5 %) as an off-white solid from CH_3CN/Et_2O: mp 180-181 °C; IR $(KBr)_{\nu max}$ 3068, 3032, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.10 (d, 1 H, J = 2.1 Hz), 8.58 (s, 1 H), 8.28 (d, 1 H, J = 9.9 Hz), 7.77 (dd, 1 H, J = 2.1, 9.9 Hz), 4.15 (s, 3 H), 3.28 (septet, 1 H, J = 6.9 Hz), 3.14 (s, 3 H), 3.02 (s, 3 H), 1.43 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 153.11, 145.49, 143.40, 137.49, 130.52, 121.77, 112.09, 111.40, 37.10, 36.84, 33.04, 24.96, 21.55. Anal. Calcd for $C_{14}H_{20}IN_3O_2$: C, 43.20; H, 5.18; N, 10.80. Found: C, 43.04; H, 5.23; N, 10.79.

1-Methyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Chloride (4) PN-III-220

To a mixture of **4b** (1.0 g, 6.8 mmol) in dry THF (15 mL) and HMPT (2.35 mL, 13.5 mmol) was added slowly N,N-dimethylcarbamoyl chloride (1.24 mL, 13.5 mmol). The reaction mixture was stirred at 60 °C overnight, then cooled in an ice bath. Solvent was carefully removed by pipette and the solid was washed with ether and dried. Recrystallization of the crude in CH_3CN/ether gave **4** (1.38 g, 80 %) as a gray solid: mp 149-151 °C; ^1H NMR ($CDCl_3$) δ 8.90 (d, 1 H, J = 2.0 Hz), 8.12 (d, 1 H, J = 2.0 Hz), 8.07 (d, 1 H, J = 9.0 Hz), 8.00 (dd, 1 H, J = 7.7, 9.0 Hz), 7.32 (d, 1 H, J = 7.7 Hz), 4.42 (s, 3 H), 3.29 (s, 3 H), 3.12 (s, 3 H). Anal. Calcd for $C_{11}H_{14}ClN_3O_2$: C, 51.67; H, 5.52; Cl, 13.86; N, 16.43. Found: C, 51.43; H, 5.59; Cl, 13.73; N, 16.34.

1-Methyl-2-(2-propyl)-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (5) PN-IV-36

Following the general procedure for quaternization, **5b** (70 mg, 0.28 mmol) was treated with methyl iodide (excess) in THF (2 mL) to give **5** (99 mg, 96 %) as white needles from CH_3CN/Et_2O: mp 155-6 °C; IR (KBr) $_{\nu max}$ 3103, 3053, 1749, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (d, 1 H, J = 9.0 Hz), 8.04 (dd, 1 H, J = 7.8, 9.0 Hz), 7.74 (s, 1 H), 7.32 (d, 1 H, J = 7.8 Hz), 4.21 (s, 3 H), 3.34 - 3.42 (m, 1 H), 3.33 (s, 3 H), 3.12 (s, 3 H), 1.48 (d, 6 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 150.06, 145.47, 141.95, 140.49, 134.92, 107.92, 107.57, 106.10, 37.57, 37.48, 33.33, 24.71, 21.40. Anal. Calcd for $C_{14}H_{20}IN_3O_{2.1/2}H_2O$: C, 42.22; H, 5.32 ; N, 10.55. Found: C, 42.19; H, 5.36; N, 10.45.

1-Methyl-2-phenyl-5-(N,N-dimethylcarbamoyloxy)imidazo[1,2-a]pyridinium Iodide (6) PN-III-236

Following the general procedure for quaternization, the reaction of **6b** (0.78 g, 2.8 mmol) with an excess of methyl iodide in dry THF (5 mL) gave **6** (0.92 g, 78.5 %) as white needles from $(CH_3)_2CO/Et_2O$: mp 156-157 °C; IR $(KBr)_{\nu max}$ 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.16 (d, 1 H, J = 9.0 Hz), 8.04 (dd, 1 H, J = 8.0, 9.0 Hz), 7.96 (s, 1 H), 7.71-7.75 (m, 2 H), 7.57 - 7.62 (m, 3 H), 7.36 (dd, 1 H, J = 0.6, 8.0 Hz), 4.15 (s, 3 H), 3.29 (s, 3 H), 3.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.22, 142.09, 140.90, 138.93, 135.35, 131.22, 130.29, 129.38, 124.28, 108.76, 108.16, 108.04, 37.58, 34.18. Anal. Calcd for: $C_{17}H_{18}IN_3O_2$: C, 48.24; H, 4.29; N, 9.93. Found: C, 48.08; H, 4.32; N, 9.93.

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